

Syndrome of the month

Marfan syndrome

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It is almost a century since Dr Antoine Bernard Marfan (1858-1942) presented Gabrielle P to the Medical Society of Paris in 1896¹ and the understanding of the condition which carries his name continues to expand. Various descriptions of similar syndromes predate that of Marfan. Williams² and Conan-Doyle in his *A study in scarlet*³ may, in fact, have recognised the disorder before Marfan. With the advantage of retrospect, various figures including Paganini⁴ and more recently Abraham Lincoln⁵ have been proposed to have suffered from Marfan syndrome. McKusick⁶ gave a classic account of the clinical features of the disorder in the first edition of *Heritable disorders of connective tissue*.

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Clinical features of Marfan syndrome

SKELETAL SYSTEM

Various analyses of affected patients have emphasised the presence of dolichocephaly and elongation of the extremities (fig 1), most marked in the fingers and toes (fig 2).⁷⁻⁹ Height and span have been measured by various workers,^{6,10,11} concluding that simple assessment of span being greater than height is of no value, as this can be observed in approximately 59% of normal males and 21% of females.¹¹ Of more value is the observation that a span exceeding height by greater than 8 cm is only observed in 5.6% of normal patients.¹¹

It is currently suggested by some workers that in the absence of confounding factors, such as vertebral deformity causing a loss of height, a span to height ratio of greater than 1.03 can be considered significant.¹²

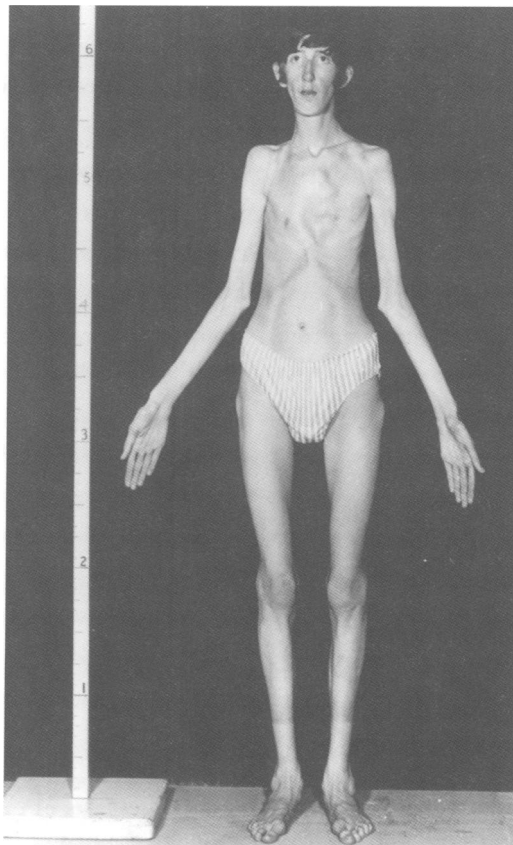


Figure 1 Clinical phenotype: dolichostenomelia, abnormal upper/lower segment ratio, and span greater than height.

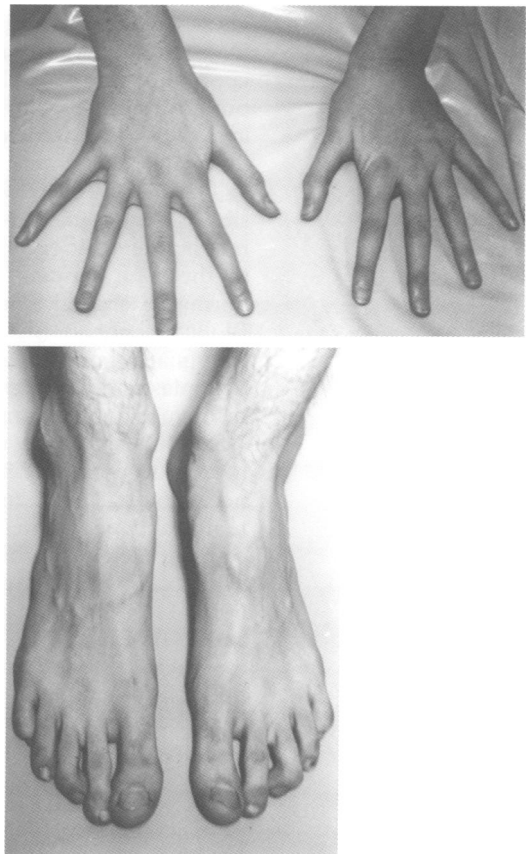


Figure 2 Arachnodactyly of the hands and feet.

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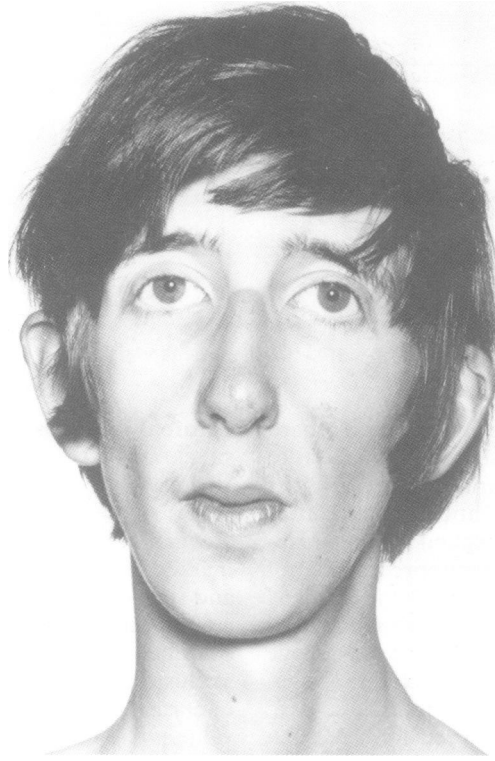


Figure 3 Typical facial features: dolichocephaly and malar hypoplasia.

Abnormal limb length is often estimated in terms of an upper segment to lower segment ratio, lower segment being measured from the top of the symphysis pubis to the floor, the upper segment being defined as total height minus the lower segment. The upper segment to lower segment ratio typically in the normal adult population is approximately 0.93 while in an adult Marfan syndrome patient it would approximate to 0.85. This ratio varies with age, but for Marfan syndrome patients it is typically at least two standard deviations below the mean for age, sex, and race.¹³

The mean height is greater than unaffected sibs or the population average for sex, age, and race and tends to run slightly above and parallel to the 97th centile.¹⁴ The skull is often abnormally shaped, being long and narrow (dolichocephaly) (fig 3). A prominent brow, retrognathic or hypognathic mandible, and a hypoplastic malar region all may contribute to the lugubrious appearance described by McKusick.¹⁵ The palate is usually high arched and narrow leading to dental overcrowding often necessitating orthodontic intervention. Vertebral and pectus deformities are a common cause of skeletal morbidity (fig 4) with scoliosis/kyphoscoliosis occurring in between 30 and 60% of Marfan syndrome patients¹⁵ at any time before skeletal maturity.

Joint laxity is common but may coexist with normal mobility or even joint contractures. Recurrent joint dislocation may result from redundant weak joint capsules, ligaments, tendons, and fascia.¹⁶

OCULAR FEATURES

Myopia is frequent, appears early, and is often severe. Monitoring of vision in childhood is

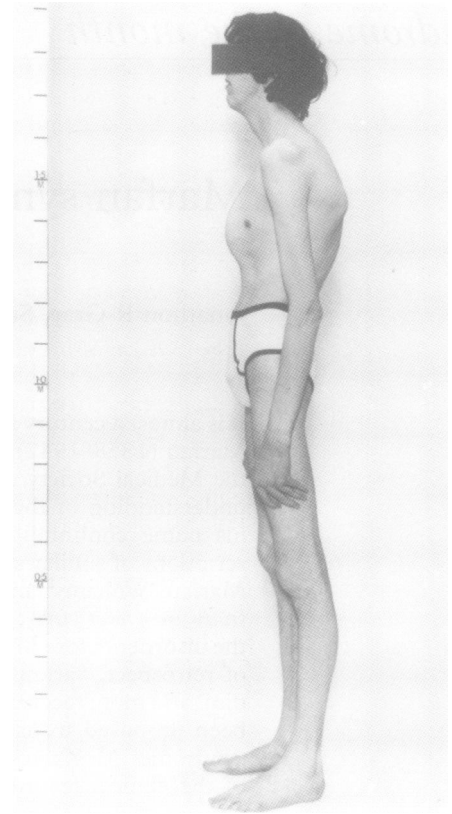


Figure 4 Kyphoscoliosis.

crucial as subsequent amblyopia is a common cause of poor vision. Blindness may also be caused by varying degrees of retinal detachment. Approximately 60% of Marfan syndrome patients¹⁷ show lens dislocation to varying degrees and in the majority of cases this is bilateral. The lens may dislocate into the anterior chamber causing acute glaucoma in a minority of cases.

CARDIOVASCULAR FEATURES

Maximum stress is applied to the first part of the ascending aorta. The first large increase in volume, and hence decrease in stress, beyond this point is at the innominate artery. As a consequence of these haemodynamic factors this is the area at which dissection and dilatation usually occurs. Dilatation usually precedes the development of an aneurysm. Some degree of dilatation can be seen in approximately 50% of children and 70 to 80% of adults with Marfan syndrome.¹⁸ The pattern of dilatation is of some value in predicting prognosis.¹⁹ The more generalised, the more serious the probable outcome, and the more generalised pattern tends to occur more in males than in females. The advent of echocardiography has made a major impact on the diagnosis and management of the cardiovascular features of Marfan syndrome. The diameter of the aortic root is measured at the level of the sinuses of Valsalva and compared to the body surface area nomograms.²⁰ Approximately 5% of cases are not adequately assessed by echocardiography because of pectus deformity.

Aortic dissection

Aortic dissection has been described at aortic diameters under 5 cm but the usual pattern is of gradual dilatation starting in the aortic root and often extending up into the ascending aorta.¹² There tends then to be a sudden onset of aortic dissection with characteristic clinical features of acute, anterior chest pain, often described as being tearing in character. The pain may radiate through to the back or up to the jaw; very occasionally the dissection may be painless.²¹ The pattern of dissection is usually of distal progression, the minority that extend proximally may interfere with the coronary circulation with disastrous results.

Mitral valve disease

Multivalvular abnormalities are the more frequent cardiac pathology in children compared to aortic complications in adults.²² Mitral valve disease is often the earliest of the cardiovascular manifestations in Marfan syndrome. On echocardiographic assessment, 80% of patients regardless of age or sex show evidence of prolapse of at least the posterior mitral valve leaflet and often show evidence of valvular redundancy.²² Mitral valve prolapse occurring in Marfan syndrome is similar to the more commonly found isolated mitral valve prolapse in that they both show increased prevalence in females and an increased prevalence with age. Differences between these two forms of mitral valve prolapse include the fact that over one-quarter of Marfan syndrome patients with mitral valve prolapse progress to mitral regurgitation by adulthood.²³

Aortic valve

Aortic regurgitation is common, progressive, and found in up to 70% of adult Marfan syndrome patients.²⁴

OTHER SYSTEM INVOLVEMENT

Striae atrophica have been reported in approximately two-thirds of patients.¹² The pathology of the striae in Marfan syndrome is identical to stretch marks found in non-Marfan syndrome patients, the most obvious abnormality being elastic fibre fragmentation.^{25,26}

Hernias are seen frequently, the most usual being inguinal, either congenital or acquired. The value of knowing the patient's diagnosis is that reinforcement of a repair with prosthetic mesh work reduces the significant risk of recurrence after surgery.¹²

The major respiratory problem in Marfan syndrome is spontaneous pneumothorax²⁷ which may be recurrent owing to rupture of apical bullae.

The spinal canal is often abnormally wide, with laminal thinning secondary to dural ectasia.²⁸ Dural ectasia is an abnormal protrusion of the dural membranes which rarely may be associated with pressure effects. It is diagnosed by CT scan, and hence not routinely assessed in the absence of suggestive symptoms such as nerve root irritation.

Table 1 A summary of the Marfan syndrome criteria according to the Berlin Nosology 1987.²⁹ In the absence of a definitely affected relative there should be skeletal involvement plus involvement of two other systems, at least one of which shows a cardinal feature (*)

Cardiovascular	Dilatation of the ascending aorta* Aortic dissection* Mitral regurgitation Calcification of mitral annulus Mitral valve prolapse Abdominal aortic aneurysm Dysrhythmia
Ophthalmological	Ectopia lentis* Flat cornea Elongated globe Retinal detachment Severe myopia
Neurological	Dural ectasia* Learning disability (verbal-performance discrepancy)
Respiratory skin/ integument	Pneumothorax Striae Hernia
Skeletal	Chest wall deformity Dolichostenomelia not resulting from scoliosis Arachnodactyly Vertebral column deformity Tall stature, especially compared to first degree relatives High, narrow arched palate Protrusio acetabulae Abnormal joint mobility

Diagnostic criteria for Marfan syndrome

In the absence of an unequivocally affected first degree relative there should be involvement of the skeleton and at least two other systems, at least one of those systems showing a major manifestation.

In the presence of at least one unequivocally affected first degree relative there should be at least two systems involved, preferably one of those systems showing a major manifestation, but this depending somewhat on the family's phenotype.²⁹

Table 1 shows the varied manifestations; those designated "major" manifestations at the conference are indicated by an asterisk.

Differential diagnosis of Marfan syndrome

It is important to consider both syndromes sharing a similar multisystem involvement to Marfan syndrome and those which may present with a single system showing Marfan-like characteristics (table 2).

A recent population based study of Marfan syndrome in the UK derived a minimum prevalence figure of 1 in 14 217 (7.03 per 100 000 population) and an incidence of 1 in 9802.³⁰ Marfan syndrome may cause death or severe handicap through adulthood and it may be anticipated to reduce reproductive fitness. Calculated reproductive fitness was 0.647.³⁰ Eight of 30 cases in the prevalence study group were assumed to be new mutations. Mutation rate was estimated at between $1.5 \pm 6.7 \times 10^{-5}$, and $1.8 \pm 7.3 \times 10^{-5}$ per haploid genome per generation.³⁰ This figure agrees with other widely quoted estimates of between 25% and 35% of cases.²² There was no evidence of an advanced paternal age effect as described by other workers.³¹

Table 2 Differential diagnosis of Marfan syndrome

Multisystem	Homocystinuria, Stickler syndrome, Ehlers-Danlos syndrome (EDS)
Skeletal	Homocystinuria, congenital contractural arachnodactyly (CCA), myotonic dystrophy, Sotos syndrome, Marfanoid hypermobility syndrome, Klinefelter syndrome, sickle cell anaemia, Stickler syndrome, multiple endocrine neoplasia type II (MEN type II), familial mitral valve prolapse syndrome, X linked mental retardation with a Marfan-like habitus
Ocular	Homocystinuria, familial ectopia lentis, Weill-Marchesani syndrome, EDS type VI, Stickler syndrome
Cardiovascular	EDS variants, familial bicuspid aortic valve, familial annuloaortic ectasia, familial mitral valve prolapse

Natural history and management

NEWBORN

Cardiovascular features may be gross especially in "neonatal Marfan syndrome" cases where various atypical features of skin laxity and contractures are associated with usually fatal cardiovascular complications and long, thin, spindly physiques. In infancy dislocated lenses are often the first diagnostic feature. Children are examined by echocardiography along with the parents if it is the first case recognised in a family. Skeletal examination allows the recording and assessment of length, weight, and habitus which may be classical, and in some infants marked pectus deformity can be detected at an early stage.

PRESCHOOL TO PUBERTY

Echocardiography is performed annually looking especially for valvular lesions which are the predominant cardiovascular abnormalities in this age group. Antibiotic prophylaxis may be indicated. β -blocker therapy may be considered for children in this age group especially in the presence of dilatation of the aorta, a severe cardiac family history, and in the absence of the usual contraindications.

Myopia may be progressive and severe and a regular assessment is important. Regular assessment of potentially progressive skeletal abnormalities such as scoliosis, kyphosis, and pectus deformity is vital for appropriate intervention. Joint laxity can be assessed, and measures such as splinting introduced. Counselling regarding appropriate careers and sports is vital. It is valuable to discuss at an early stage how interview panels for the armed forces, police,

and other such careers may not consider an applicant with Marfan syndrome to be physically suitable. Contact sports are discouraged to try and reduce the risk of lens dislocation and also associated shear forces across a potentially dilated aortic root. Similarly discouraged are sports and occupations causing sudden increases in blood pressure, for example, explosive type sports and occupations requiring heavy manual labour.

PUBERTY

Rapid body growth brings the risk of progressive aortic dilatation and annual or even six monthly echocardiograms may be necessary. Spinal abnormalities may accelerate and should be carefully checked for on each visit. The psychosocial aspects of the disorder may need to be addressed, with a careful discussion of coping with issues such as anger or unkind comments from peers. Discussion of the genetic basis of the disorder will be necessary, both individually and with partners in the later years. The extra care needed in managing pregnant Marfan patients should be explained.

ADULTHOOD

Annual echocardiography is usually adequate, although more frequent assessment may be necessary if aortic dilatation is progressing rapidly. In the absence of abnormality, regular ophthalmological assessment is not necessary but emphasis must be placed on seeking urgent ophthalmic referral if vision deteriorates suddenly. Annual clinic visits allow monitoring of progress, discussion of echocardiogram results, and continuing career/exercise advice, and are very useful for pre- and postsurgical counselling if aortic replacement is contemplated.

Prenatal

With the availability of linkage analysis for some suitable families and mutation detection in a minority, the issues of screening can be addressed. It is clear that families are keen to undertake presymptomatic and prenatal testing for Marfan syndrome where feasible.³²

Life expectancy

Life expectancy has improved, most probably because of early diagnosis and appropriate surveillance and intervention.³³ β -blockers seem likely to confer an improved prognosis³⁴ although the optimum age for beginning is uncertain. In many centres, including our own, appropriate β -blockade would be started at the first signs of aortic dilatation, as assessed using standardised reference ranges for age and sex. Other centres prefer to start β -blocker therapy at an earlier stage in the disease course, hoping to intervene before dilatation starts. Surgical techniques in appropriate specialised centres have undoubtedly also contributed to the improved life expectancy. Our data (unpublished) suggest that life expectancy has increased (fig 5) and for counselling purposes we suggest

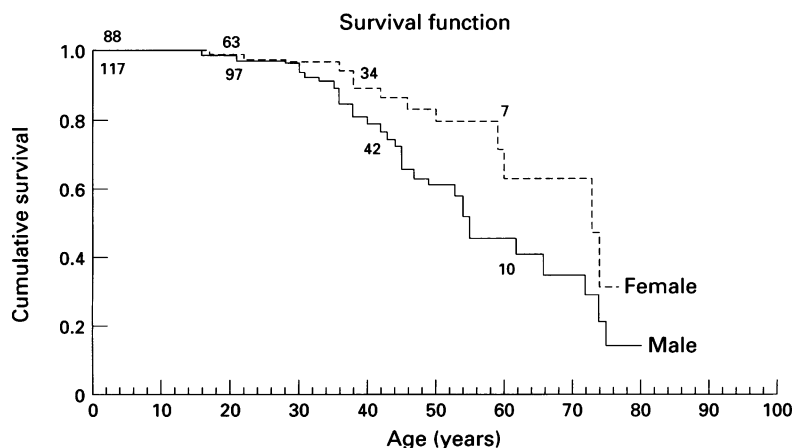


Figure 5 Mortality curves for British Marfan syndrome patients. Kaplan Meir survival curves for a cohort of Marfan syndrome patients with regard to gender (unpublished).

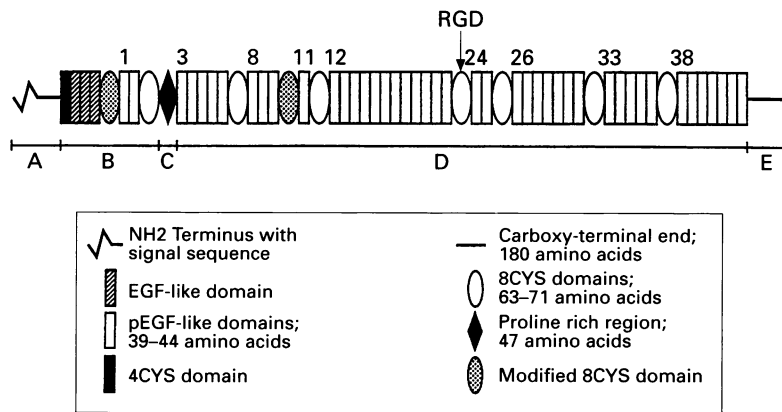


Figure 6 Diagrammatic representation of the proposed amino acid structure of human fibrillin.

in British populations the mean cumulative probability of survival for men is 53 years and for women 72 years. The average age at death for our British patients is 44 years for men and 47 years for women.

Genetics

The autosomal dominant inheritance of Marfan syndrome has been well established with between 25 and 30% of cases being new mutations.²² Initial evidence for the involvement of various collagens was discounted by linkage studies.^{35,36} The discovery in 1986 of a new glycoprotein named fibrillin³⁷ and its ubiquitous distribution within both elastic and non-elastic tissues in the body led to the suspicion of the involvement of fibrillin in the pathological process causing Marfan syndrome. In 1991, in a good example of the convergence of separate approaches, linkage of Marfan syndrome was established to chromosome 15q³⁸ at the same time as immunofluorescent imaging showed reduced levels of fibrillin to be present in fibroblast preparations from Marfan syndrome patients.³⁹ As sequence of the gene became available, mutations were described.⁴⁰ The fibrillin gene itself is a complex multi-domain structure containing EGF (epidermal growth factor)-like repeats, TGF (transforming growth factor)-like domains, and also unique hybrid domains which bear resemblance to both EGF and TGF motifs. The gene is large, 110 kb with 56 exons and 10 kb of coding sequence. The entire sequence is now established and nonsense and missense mutations as well as deletions and insertions have been detected. However, despite this knowledge mutation analysis has proved disappointing and time consuming with only a poor yield of mutations, most appearing unique. Genotype/phenotype correlation is proving difficult with only the occurrence of mutations clustering within EGF motifs 24-26⁴¹ in several severe, sporadic, neonatal Marfan patients appearing to show a consistent pattern. The EGF repeats have six crucial cysteine residues which appear vital for disulphide bonding leading to stable β sheet formation and intracellular processing as well as aiding calcium binding by the highly conserved consensus calcium binding sites

within the calcium binding EGF, TGF, and hybrid motifs. The commonest mutations described to date are point mutations of these cysteine residues.

Protein biochemistry has shown alterations in the synthesis, secretion, and processing of fibrillin in cell lines from patients with Marfan syndrome.⁴² These variations in patients with differing severity of phenotype have led to the suggestion of a dominant negative mechanism with severity of phenotype being dependent on the level of mutant product expressed.⁴³ However, the report of a null allele associated with a severe phenotype is hard to equate with a dominant negative effect.⁴⁴

Fibrillin (fig 6) is secreted as a 350 kDa profibrillin and processed extracellularly into fibrillin which forms higher molecular weight aggregates.⁴⁵ It is the vital component of the ubiquitous 10 nm microfibril which interacts with elastin in elastic fibres within tissues, such as the aorta and ligaments, or serves an anchoring function in non-elastic tissues, such as the ciliary zonules, bone periosteum, and tendon. Rotary shadowing electron microscopic studies of microfibrils assembled by tissue in cell culture confirms the extracellular aggregation and assembly of fibrillin molecules into 10 nm diameter microfibrils with a beaded structure and a constant periodicity of 50-55 nm. Studies of cell lines from patients with Marfan syndrome confirm abnormalities in microfibrillar assembly.⁴⁶ Subsequently, the fibrillin gene identified on chromosome 15 has been shown to be part of a larger "gene family". At least three other fibrillin-like genes exist. A second locus has been mapped to chromosome 3,⁴⁷ although there is some dispute whether the phenotype is truly consistent with Marfan syndrome. Fibrillin homologues have been identified on chromosomes 5 and 17.^{48,49} With the elucidation of respective sequences, polymorphic intragenic markers have allowed disease entities similar to Marfan syndrome to be tested at these loci. Despite the difficulties of describing a family's phenotype as being "pure" ectopia lentis, linkage for such families has been described for chromosome 15.⁴⁸ The disorder congenital contractural arachnodactyly has been linked to fibrillin-5.⁴⁸ Recently the gene encoding microfibril associated glycoprotein (MAGP) has been mapped to 15q⁵⁰ and it is possible that mutations within this gene may be responsible for phenocopies of Marfan syndrome and explain the low mutation detection rate in Marfan families.

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